

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

SCHEDULE 13G

UNDER THE SECURITIES EXCHANGE ACT OF 1934
(AMENDMENT NO. 8)*

Isis Pharmaceuticals, Inc.

(Name of Issuer)

Common Stock

(Title of Class of Securities)

464330-10-9

(CUSIP Number)

December 31, 2005

(Date of Event Which Requires Filing of this Statement)

Check the appropriate box to designate the rule pursuant to which this Schedule is filed:

/X/ Rule 13d-1(b)
/ / Rule 13d-1(c)
/ / Rule 13d-1(d)

*The remainder of this cover page shall be filled out for a reporting person's initial filing on this form with respect to the subject class of securities, and for any subsequent amendment containing information which would alter the disclosures provided in a prior cover page.

The information required in the remainder of this cover page shall not be deemed to be "filed" for the purpose of Section 18 of the Securities Exchange Act of 1934 ("Act") or otherwise subject to the liabilities of that section of the Act but shall be subject to all other provisions of the Act (however, see the Notes).

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SCHEDULE 13G

CUSIP NO. 464330-10-9

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(1) NAMES OF REPORTING PERSONS
I.R.S. IDENTIFICATION NOS. OF ABOVE PERSONS (ENTITIES ONLY)

Citigroup Global Markets Inc.

(2) CHECK THE APPROPRIATE BOX IF A MEMBER OF A GROUP (SEE INSTRUCTIONS)

(a) / /
(b) / /

(3) SEC USE ONLY

(4) CITIZENSHIP OR PLACE OF ORGANIZATION

New York

NUMBER OF	(5) SOLE VOTING POWER	0
SHARES		
BENEFICIALLY	(6) SHARED VOTING POWER	719,506*
OWNED BY		**
EACH	(7) SOLE DISPOSITIVE POWER	0
REPORTING		
PERSON	(8) SHARED DISPOSITIVE POWER	719,506*
WITH:		**
(9) AGGREGATE AMOUNT BENEFICIALLY OWNED BY EACH REPORTING PERSON		719,506*
		**

(10) CHECK IF THE AGGREGATE AMOUNT IN ROW (9) EXCLUDES CERTAIN SHARES (SEE INSTRUCTIONS) / /

(11) PERCENT OF CLASS REPRESENTED BY AMOUNT IN ROW (9) 1.0%*

**

(12) TYPE OF REPORTING PERSON (SEE INSTRUCTIONS) BD

* Prior to the sale of the Asset Management division of Citigroup Global Markets Inc. to Legg Mason, Inc. effective as of December 1, 2005 (the "Sale"), Citigroup Global Markets Inc., Citigroup Financial Products Inc., Citigroup Global Markets Holdings Inc. and Citigroup Inc. (collectively, the "Reporting Persons") beneficially owned more than 5% of the Issuer's securities. Upon completion of the Sale, the Reporting Persons no longer beneficially owned more than 5% of the Issuer's securities.

** Assumes conversion/exercise of certain securities held.

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(1) NAMES OF REPORTING PERSONS
I.R.S. IDENTIFICATION NOS. OF ABOVE PERSONS (ENTITIES ONLY)

Citigroup Financial Products Inc.

(2) CHECK THE APPROPRIATE BOX IF A MEMBER OF A GROUP (SEE INSTRUCTIONS)

(a) / /

(b) / /

(3) SEC USE ONLY

(4) CITIZENSHIP OR PLACE OF ORGANIZATION Delaware

NUMBER OF	(5) SOLE VOTING POWER	0
SHARES		
BENEFICIALLY	(6) SHARED VOTING POWER	738,506*
OWNED BY		**
EACH	(7) SOLE DISPOSITIVE POWER	0

REPORTING

PERSON (8) SHARED DISPOSITIVE POWER 738,506*
**

WITH:

(9) AGGREGATE AMOUNT BENEFICIALLY OWNED BY EACH REPORTING PERSON 738,506*
**

(10) CHECK IF THE AGGREGATE AMOUNT IN ROW (9) EXCLUDES CERTAIN SHARES (SEE INSTRUCTIONS) / /

(11) PERCENT OF CLASS REPRESENTED BY AMOUNT IN ROW (9) 1.0%*
**

(12) TYPE OF REPORTING PERSON (SEE INSTRUCTIONS) CO

* Prior to the Sale, the Reporting Persons beneficially owned more than 5% of the Issuer's securities. Upon completion of the Sale, the Reporting Persons no longer beneficially owned more than 5% of the Issuer's securities.

** Assumes conversion/exercise of certain securities held.

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(1) NAMES OF REPORTING PERSONS
I.R.S. IDENTIFICATION NOS. OF ABOVE PERSONS (ENTITIES ONLY)

Citigroup Global Markets Holdings Inc.

(2) CHECK THE APPROPRIATE BOX IF A MEMBER OF A GROUP (SEE INSTRUCTIONS)

(a) / /
(b) / /

(3) SEC USE ONLY

(4) CITIZENSHIP OR PLACE OF ORGANIZATION New York

NUMBER OF (5) SOLE VOTING POWER 0
SHARES

BENEFICIALLY (6) SHARED VOTING POWER 741,721*
**

OWNED BY

EACH (7) SOLE DISPOSITIVE POWER 0

REPORTING

PERSON (8) SHARED DISPOSITIVE POWER 741,721*
**

WITH:

(9) AGGREGATE AMOUNT BENEFICIALLY OWNED BY EACH REPORTING PERSON 741,721*

 (10) CHECK IF THE AGGREGATE AMOUNT IN ROW (9) EXCLUDES CERTAIN SHARES (SEE INSTRUCTIONS) / /

 (11) PERCENT OF CLASS REPRESENTED BY AMOUNT IN ROW (9) 1.0%*
 **

 (12) TYPE OF REPORTING PERSON (SEE INSTRUCTIONS) HC

 * Prior to the Sale, the Reporting Persons beneficially owned more than 5% of the Issuer's securities. Upon completion of the Sale, the Reporting Persons no longer beneficially owned more than 5% of the Issuer's securities.

** Assumes conversion/exercise of certain securities held.

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 (1) NAMES OF REPORTING PERSONS
 I.R.S. IDENTIFICATION NOS. OF ABOVE PERSONS (ENTITIES ONLY)

Citigroup Inc.

 (2) CHECK THE APPROPRIATE BOX IF A MEMBER OF A GROUP (SEE INSTRUCTIONS)

(a) / /

(b) / /

 (3) SEC USE ONLY

 (4) CITIZENSHIP OR PLACE OF ORGANIZATION Delaware

 NUMBER OF (5) SOLE VOTING POWER 0
 SHARES

 BENEFICIALLY (6) SHARED VOTING POWER 768,458*
 **

 OWNED BY
 EACH (7) SOLE DISPOSITIVE POWER 0

 REPORTING
 PERSON (8) SHARED DISPOSITIVE POWER 768,458*
 **

WITH:

 (9) AGGREGATE AMOUNT BENEFICIALLY OWNED BY EACH REPORTING PERSON 768,458*
 **

 (10) CHECK IF THE AGGREGATE AMOUNT IN ROW (9) EXCLUDES CERTAIN SHARES (SEE INSTRUCTIONS) / /

(12) TYPE OF REPORTING PERSON (SEE INSTRUCTIONS)

HC

* Prior to the Sale, the Reporting Persons beneficially owned more than 5% of the Issuer's securities. Upon completion of the Sale, the Reporting Persons no longer beneficially owned more than 5% of the Issuer's securities.

** Assumes conversion/exercise of certain securities held.

*** Includes shares held by the other reporting persons.

Item 1(a). Name of Issuer:

Isis Pharmaceuticals, Inc.

Item 1(b). Address of Issuer's Principal Executive Offices:

1896 Rutherford Road
Carlsbad, CA 92008

Item 2(a). Name of Person Filing:

Citigroup Global Markets Inc. ("CGM")
Citigroup Financial Products Inc. ("CFP")
Citigroup Global Markets Holdings Inc. ("CGM Holdings")
Citigroup Inc. ("Citigroup")

Item 2(b). Address of Principal Office or, if none, Residence:

The address of the principal office of each of
CGM, CFP and CGM Holdings is:

388 Greenwich Street
New York, NY 10013

The address of the principal office of Citigroup is:

399 Park Avenue
New York, NY 10043

Item 2(c). Citizenship or Place of Organization:

CGM and CGM Holdings are New York corporations.

CFP and Citigroup are Delaware corporations.

Item 2(d). Title of Class of Securities:

Common Stock

Item 2(e). CUSIP Number:

464330-10-9

Item 3. If This Statement is Filed Pursuant to Sections 240.13d-1(b) or 240.13d-2(b) or (c), Check Whether the Person Filing Is a(n):

- (a) Broker or dealer registered under Section 15 of the Act (15 U.S.C. 78o);
- (b) Bank as defined in Section 3(a)(6) of the Act (15 U.S.C. 78c);
- (c) Insurance company as defined in Section 3(a)(19) of the Act (15 U.S.C. 78c);
- (d) Investment company registered under Section 8 of the Investment Company Act of 1940 (15 U.S.C. 80a-8);

- (e) [] Investment adviser in accordance with Section 240.13d-1(b)(1)(ii)(E);
- (f) [] Employee benefit plan or endowment fund in accordance with Section 240.13d-1(b)(1)(ii)(F);
- (g) [X] Parent holding company or control person in accordance with Section 240.13d-1(b)(1)(ii)(G);
- (h) [] Savings association as defined in Section 3(b) of the Federal Deposit Insurance Act (12 U.S.C. 1813);
- (i) [] Church plan that is excluded from the definition of an investment company under Section 3(c)(14) of the Investment Company Act of 1940 (15 U.S.C. 80a-3);
- (j) [] Group, in accordance with Section 240.13d-1(b)(1)(ii)(J).

Item 4. Ownership. (as of December 31, 2005)

- (a) Amount beneficially owned: See item 9 of cover pages
- (b) Percent of Class: See item 11 of cover pages
- (c) Number of shares as to which the person has:
 - (i) Sole power to vote or to direct the vote:
 - (ii) Shared power to vote or to direct the vote:
 - (iii) Sole power to dispose or to direct the disposition of:
 - (iv) Shared power to dispose or to direct the disposition of:

See Items 5-8 of cover pages

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Item 5. Ownership of Five Percent or Less of a Class.

If this statement is being filed to report the fact that as of the date hereof the reporting person has ceased to be the beneficial owner of more than five percent of the class of securities, check the following [X].

Item 6. Ownership of More Than Five Percent on Behalf of Another Person.

Not Applicable.

Item 7. Identification and Classification of the Subsidiary which Acquired the Security being Reported on by the Parent Holding Company.

CFP is the sole stockholder of CGM. CGM Holdings is the sole stockholder of CFP. Citigroup is the sole stockholder of CGM Holdings.

Item 8. Identification and Classification of Members of the Group.

Not Applicable.

Item 9. Notice of Dissolution of Group.

Not Applicable.

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Item 10. Certification.

By signing below I certify that, to the best of my knowledge and belief, the securities referred to above were acquired and are held in the

ordinary course of business and were not acquired and are not held for the purpose of or with the effect of changing or influencing the control of the issuer of the securities and were not acquired and are not held in connection with or as a participant in any transaction having that purpose or effect.

SIGNATURE.

After reasonable inquiry and to the best of my knowledge and belief, I certify that the information set forth in this statement is true, complete and correct.

Dated: January 5, 2006

CITIGROUP GLOBAL MARKETS INC.

By: /s/ Ali L. Karshan

Name: Ali L. Karshan
Title: Assistant Secretary

CITIGROUP FINANCIAL PRODUCTS INC.

By: /s/ Ali L. Karshan

Name: Ali L. Karshan
Title: Assistant Secretary

CITIGROUP GLOBAL MARKETS HOLDINGS INC.

By: /s/ Ali L. Karshan

Name: Ali L. Karshan
Title: Assistant Secretary

CITIGROUP INC.

By: /s/ Ali L. Karshan

Name: Ali L. Karshan
Title: Assistant Secretary

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EXHIBIT INDEX TO SCHEDULE 13G

EXHIBIT 1

- - - - -

Agreement among CGM, CFP, CGM Holdings and Citigroup as to joint filing of Schedule 13G.

EXHIBIT 1

AGREEMENT AS TO JOINT FILING OF SCHEDULE 13G

Each of the undersigned hereby affirms that it is individually eligible to use Schedule 13G, and agrees that this Schedule 13G is filed on its behalf.

Date: January 5, 2006

CITIGROUP GLOBAL MARKETS INC.

By: /s/ Ali L. Karshan

Name: Ali L. Karshan
Title: Assistant Secretary

CITIGROUP FINANCIAL PRODUCTS INC.

By: /s/ Ali L. Karshan

Name: Ali L. Karshan
Title: Assistant Secretary

CITIGROUP GLOBAL MARKETS HOLDINGS INC.

By: /s/ Ali L. Karshan

Name: Ali L. Karshan
Title: Assistant Secretary

CITIGROUP INC.

By: /s/ Ali L. Karshan

Name: Ali L. Karshan
Title: Assistant Secretary